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PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

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PCT

INVITATION TO PAY ADDITIONAL FEES

(PCT Article 17(3)(a) and Rule 40.1)

Applicant's or agent's file reference 28383	Date of Mailing *(day/month/year)* 27 January 2006 (d) PAYMENT DUE within 15 days from the above date of mailing
International application No. PCT/IL04/01046	International filing date *(day/month/year)* 15 November 2004 (15.11.2004)
Applicant TECHNION RESEARCH & DEVELOPMENT FOUNDATION LTD.	

1. This International Searching Authority

(i) considers that there are 4 *(number of)* inventions claimed in the international application covered by the claims indicated below/on an extra sheet:
Please See Continuation Sheet

and it considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated below/on an extra sheet:
Please See Continuation Sheet

(ii) ☐ has carried out a partial international search (see Annex) ☒ will establish the international search report on those parts of the international application which relate to the invention first mentioned in claims Nos.: 1-11

(iii) will establish the international search report on the other parts of the international application only if, and to the extent to which, additional fees are paid.

2. The applicant is hereby invited, within the time limit indicated above, to pay the amount indicated below:

$1,000.00	X 3	= $3,000.00
Fee additional per invention	number of additional inventions	total amount of additional fees

The applicant is informed that, according to Rule 40.2(c), the payment of any additional fee may be made under protest, i.e., a reasoned statement to the effect that the international application complies with the requirement of unity of invention or that the amount of the required additional fee is excessive.

3. ☐ Claim(s) Nos. _____ have been found to be unsearchable under Article 17(2)(b) because of defects under Article 17(2)(a) and therefore have not been included with any invention.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized officer Thaian N. Ton Telephone No. 571-272-0500

Form PCT/ISA/206 (July 1992)

INVITATION TO PAY ADDITIONAL FEES

International application No.
PCT/IL04/01046

This International Search Authority has found 4 inventions claimed in the International Application covered by the claims indicated below:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-11, drawn to isolated stem cells or stem cell lines carrying a disease-causing mutation in a genomic polynucleotide sequence thereof.

Group II, claim(s) 12-26, drawn to isolated embryoid bodies comprising a plurality of cells at least some of which carry a disease-causing mutation in a genomic polynucleotide sequence thereof.

Group III, claim(s) 27-34, drawn to isolated differentiated cells, tissues or organs, carrying at least one disease-causing mutation in a genomic polynucleotide sequence thereof.

Group IV, claim(s) 35-51, drawn to methods of identifying agents suitable for treating a disorder associated with at least one disease-causing mutation.

1. This International Searching Authority considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated below:
The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Unity of Invention between different categories of inventions will only be found to exist if specific combinations of inventions are present. Those combinations include:

1) A product and a special process of manufacture of said product
2) A product and a process of use of said product
3) A product, a special process of manufacture of said product, and a process of use of said product
4) A process and an apparatus specially designed to carry out said process
5) A product, a special process of manufacture of said product, and an apparatus specially designed to carry out said process.

The allowed combinations do not include multiple products, multiple methods of using said products, and methods of making multiple products as claimed in the instant invention.

The inventions are not so linked because they do not have a single general inventive concept. Groups I-III are to different products that are not required or recited for the implementation of the other. Each of these products is distinct, both structurally and functionally, and thus, has its own special technical feature. Groups I-IV lack a common special technical feature, and thus, unity of invention is found to be lacking.
The special technical feature of Group I is considered to be an isolated stem cell or stem cell line, carrying a disease-causing mutation in a genomic polynucleotide sequence. The special technical feature of Group II is considered to be an isolated embryoid body comprising a plurality of cells, wherein at least some of which carry a disease-causing mutation in a genomic polynucleotide sequence. The special technical feature of Group III is considered to be an isolated differentiated cell, tissue or organ, carrying at least one disease-causing mutation in a genomic polynucleotide sequence. The special technical feature of Group IV is considered to be a method of identifying an agent suitable for treating a disorder associated with at least one disease-causing mutation.
Groups I-IV lack a common, special technical feature because stem cells carrying a disease-causing mutation in a genomic polynucleotide sequence were well-known in the art. For example, this is evidenced by Leonard *et al.* (Immunological Reviews, 148:97-114 (1995)) who teach a mutation in the γ_c gene in mice results in various abnormalities, with similar characteristics as seen in patients suffering from X-linked severe combined immunodeficiency. See Abstract. They teach that these mice were developed by transfection of mouse ES cells, and homologous recombination to produce the knockout ES cells. These ES cells were then used to produce the knockout mice. Thus, Leonard *et al.* show a stem cell that has a mutation that causes a disease in the resultant mouse.
Thus, Groups I-IV are not so linked by the same or a corresponding special technical feature as to form a single, general inventive concept.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

(a) Distinct types of mutations, recited in claims 4, 17, 32, 40.
i) missense

ii) nonsense
iii) frameshift
iv) readthrough
v) promoter
vi) regulatory
vii) deletion
viii) insertion
ix) inversion
x) splice
xi) duplication

Distinct disease-causing mutations, recited in claims 5, 6, 18, 19, 33, 34, 41, 42

i) cystic fibrosis
ii) myotonic dystrophy
iii) van Waardenburg syndrome
iv) metachromatic leukodystrophy
v) Gorlin disease
vi) Huntington's disease
vii) Spinal muscular atrophy
viii) Duchenne muscular dystrophy
ix) SEQ ID NO: 24
x) 510del28 in SEQ ID NO: 34
xi) SEQ ID NO: 22
xii) SEQ ID NO: 21